ABSTRACT

The first known case of COVID-19 caused by the novel coronavirus now known as SARS-CoV-2 occurred in Wuhan, China in late December 2019. In a matter of a few months, it has spread globally to infect more than 500,000 people and has caused more than 20,000 deaths. It was officially declared a pandemic on March 11, 2020, by the World Health Organization (WHO). To date, it has strained medical infrastructure, stagnated global economy and given rise to social stigma, fear, and racism. In this article, we provide a comprehensive review of our current knowledge and understanding of this new disease.

Keywords: Coronavirus; SARS-CoV-2; COVID-19.
1. INTRODUCTION

By late December 2019, Chinese physicians reported a series of unexplained respiratory infections in Wuhan, Hubei, China [1-4]. The initial outbreak was linked to the Huanan Seafood Wholesale Market and involved about 66% of the staff there [1]. This was similar to the 2002 severe acute respiratory syndrome (SARS) epidemic which also started from a seafood wet market [2]. These so-called wet markets are common in parts of Asia, Africa, South America and Oceania [3]. Wet markets imply that both live and dead animals are sold. These represent an ideal environment for viral and bacterial transmission through blood, urine, feces and other biofluids that may lead to recombinant events. In addition, the presence of live animals makes it difficult to ensure meat safety. Disease transmission is further encouraged by the fact that these markets usually have subpar hygienic practices [3].

In the month following this initial outbreak, thousands of people in multiple provinces of China were affected by this fast-spreading disease and soon cases outside the country started being reported as well [1]. The underlying respiratory pathogen was identified as a novel beta-coronavirus and was provisionally named as the 2019 novel coronavirus (2019-nCoV) by the World Health Organization (WHO) [5]. The novel coronavirus pneumonia was named COVID-19, an acronym for “coronavirus disease 2019” [5]. As per established practice, the International Committee on Taxonomy of Viruses (ICTV) renamed the underlying pathogen as SARS-CoV-2 [5]. At the time of preparation of this manuscript (March, 27th 2020), COVID-19 has spread to 199 countries and territories and one international conveyance [6]. It has caused 532,262 cases and 24,090 deaths. It has dominated headlines, stagnated global economy and turned cities into ghost towns. It has also created a ripple effect of fear and hysteria that have gone on to fuel racism and stigma. In this article, we provide a comprehensive review regarding our current understanding of this new disease as well as provide a snapshot of the current global situation.

2. COVID-19 IS THE THIRD MAJOR CORONAVIRUS OUTBREAK IN THE NEW MILLENNIUM

Coronaviruses are typically low virulence organisms and lead to mild respiratory symptoms [7]. Commonly detected human coronaviruses include 229E, OC43, NL63, and HKU1 [7]. However, since the beginning of the 21st century, three coronaviruses have moved across the species barrier to cause deadly pneumonia in humans [8].

In 2002-2003, a new coronavirus, the severe acute respiratory syndrome coronavirus (SARS-CoV) originated in the Guangdong province of southeast China [1,9,10]. The disease quickly spread to five continents including countries such as Canada, the United States of America (USA), Australia, Germany, France, Sweden, the United Kingdom and Spain [9]. It infected an estimated number of 8,098 people and caused 774 deaths (around 10% fatality) [8,9]. On May 19th, 2004 the WHO declared the end to the SARS-CoV outbreak [9].

In 2012, a new outbreak occurred in the Arabian Peninsula that was subsequently named as Middle-East respiratory syndrome coronavirus (MERS-CoV) [1,8,9]. MERS-CoV is still a cause of public health concern as the risk of new cases is still not over [8,9]. It is believed to have caused approximately 2506 cases with 862 deaths in about 26 countries (around 35% fatality) [9].

The latest coronavirus, SARS-CoV-2 also originated from China. Ever since the first 41 cases reported at Wuhan, China, SARS-CoV-2 has spread globally to infect more than 300,000 people [11]. An “epidemiological alert” was raised by local authorities on December 31st, 2019 and by January 1st, 2020, the Huanan seafood market was shut down [1]. Wuhan, being a large metropolitan and a major transport hub with a population of 11 million most likely may have contributed to a quick spread of this disease to surrounding cities and provinces. The outbreak also coincided with the Chinese Lunar New Year (January 25th), presumably the largest annual human migration in the world. The first exported case was reported in Thailand on January 13th, 2020 [1]. The USA reported its first case on January 19th, 2020 in Washington state [12]. A strict metropolitan-wide quarantine was imposed on Wuhan on January 24th [2]. Due to the rapid spread, WHO raised a public health emergencies of international concern (PHEIC) alarm on January 30, 2020 [1]. On March 11, 2020, WHO officially characterized the spread of COVID-19 as a pandemic. To date, there have been 532,262 cases and 24,090 deaths (around 4.5% mortality) [6]. Using data provided by the WHO on their website we have summarized the global
situation by demonstrating total cases (Fig. 1) and deaths (Fig. 2) [13].

3. SARS-COV-2 DEMONSTRATES SEQUENCE HOMOLOGY WITH BATS, TRANSMITS THROUGH RESPIRATORY DROPLETS AND INDUCES A CYTOKINE STORM

Coronavirus is an envelope, positive single-strand RNA virus. It derives its name from the crown-like spikes on its surface [1,7,14]. It is a family of zoonotic infections - meaning that they are typically harbored in animals. It is classified under the family Coronaviridae and was first discovered in the 1960s [14]. It is further subclassified as Orthocoronavirinae and Torovirinae. The subfamily Orthocoronavirinae is further divided into alpha-, beta-, gamma- and delta-coronaviruses. Alpha- and beta-coronaviruses generally infect mammals. Gamma-coronaviruses are mostly found in avian species whereas delta-coronaviruses circulate in both birds and mammals.

Studies have demonstrated sequence homology between bat coronaviruses and SARS-CoV and MERS-CoV [1]. This has established bats as the natural reservoir for these pathogens [14]. Palm civets and raccoon dogs are thought to be the intermediate host for SARS-CoV while the dromedary camel is believed to be the intermediate host for MERS-CoV [14].

In the month following the initial outbreak in Wuhan, the novel coronavirus was isolated and sequenced by Chinese scientists who were able to obtain eight complete viral genome sequences from nine patients [2]. Sequence homology of 99.98% was observed between the eight genomes suggesting a spill-over event from an animal source to humans [2]. Sequence homology of 87.6% and 79% was observed with bat coronaviruses and SARS-CoV respectively [2,4,14]. This finding once more implicated bats as the most likely primary host for SARS-CoV-2. However, since bats were already in hibernation at the time of the outbreak and since there are no bats sold at the Huanan seafood market, the presence of an unidentified intermediate host is highly probable [2].

Both SARS-CoVs enter cells via the Angiotensin-converting enzyme 2 (ACE2) receptors found in the lower airway [4,8,10]. It has a spike (S) glycoprotein that promotes entry into cells and serves as a target for antibodies [8]. The virus is a potent inducer of inflammation [15]. The resultant cytokine storm has been postulated as the mechanism of organ damage [4].

Person to person transmission of the virus includes droplet inhalation such as cough and sneeze and contact transmission via oral, nasal and eye mucus membranes [16]. Viral RNAs have been found in nasal discharge, sputum, blood, and feces [1]. This may indicate that the fecal-oral route of transmission may be possible as well. Initial reports estimate the basic reproduction number (R0) at 2.2 (95% CI 1.4-3.9) [10]. This means that on average every infected person will pass on the pathogen to another 2.2 people.

4. THE GLOBAL SPREAD OF COVID-19 HAS ALSO FUELED A RAPID SURGE IN MISINFORMATION, FEAR AND PREJUDICE

With the rapid spread of COVID-19, fear and paranoia are the symptoms most people are afflicted with. As with all novel diseases, misinformation is common and this exacerbates panic and social stigma. Bigotry and prejudice have been common findings in the history of epidemics and COVID-19 is no different. It appears that there is a tendency to associate disease with foreignness. For example, when syphilis spread across Europe in the fifteenth century, it was known as the French pox by the English, the Naples sickness by the Florentines, morbus Germanicus by the Parisians and the Chinese disease by the Japanese [17]. Similarly, in more recent times, Latinos have been targeted for the outbreak of swine flu in 2009 and Africans for the Ebola crisis in 2014 [17].

For Covid-19, it has been referred to as the “China virus” and this has led to a string of racist attacks on people of Asian descent [18]. In Denmark, a newspaper published a cartoon of the Chinese flag and replaced its stars with virus-like drawings [17,18]. The Wall Street Journal published an article titled “China is the real sick man of Asia” [17-19]. Similarly, the Australian Herald Sun published a column headlined “China kids stay home” where it also referred to SARS-CoV-2 as the “Chinese virus” [17,18]. French papers ran articles headlined “New Yellow Peril” and “Yellow Alert” [18]. Similarly, high ranking US officials have also tried to shift blame for COVID-19 primarily to China by attacking Chinese culture and using the term “Chinese virus” [20,21].
Fig. 1. Publicly available data on the WHO website depicting COVID-19 cases in five countries against time and signifying the global spread of disease. (2020)

Fig. 2. Publicly available data on the WHO website depicting COVID-19 total deaths in five countries against time. (2020)
Fig. 3. COVID-19 patient comorbidities reported in previous studies
It is important to appreciate that stigma leads to discriminatory behavior towards people, not only afflicted by the disease but also their family members, friends and communities as well. This has a serious impact on the spread of pandemics. Due to unwarranted exclusion and persecution that the patients might face, there may be a reluctance to seek appropriate medical help [18]. Furthermore, though the virus may have originated from China, it is no longer just a Chinese issue. As highlighted above, it does not respect borders and does not discriminate on the basis of ethnicity or country. The need for solidarity among people and for leaders to curb social stigma and fear is essential if we are to overcome this common enemy.

5. FOR THE VAST MAJORITY OF PATIENTS, COVID-19 RESULTS IN A MILD FLU-LIKE ILLNESS

Table 1 summarizes the demographic findings of eleven early studies from China and South Korea [11,22-31]. Patients generally belong to the 30-79 age groups with the highest average age of 59 being reported by Li et al, and the lowest of 41 reported by Xi et al [22,23,28]. There was a slight predominance of men reported in most studies.

Hypertension was the most common comorbidity reported in all studies. Other cardiovascular comorbidities such as arrhythmias, hyperlipidemia, coronary heart disease have all been grouped together for the ease of presentation in Fig. 3. Diabetes is the most common comorbid endocrine disorder, with only Zhang et al. reporting thyroid disorders (3.6%) [24]. Respiratory disorders made up 2-4% of the coexisting illnesses – the majority of which were COPD. Chronic kidney and liver disease were also a common comorbid condition amongst patients of COVID-19 pneumonia [24,25,27,30]. Fig. 1 summarizes the patient comorbidities reported.

A study by the Chinese Center for Disease Control (CDC), consisting of 44,672 confirmed cases of COVID-19 demonstrated that the majority of patients (81%) suffer from a mild illness only [22]. They also demonstrated that 14% of the patient in their cohort had severe illness while only 5% had critical disease.

Fever is the most common symptom observed [11,22,23]. This is followed by a dry cough, malaise, dyspnea, tachypnea and chest pain [23]. It is important to note that rhinorrhea is rarely reported [26,28].

Radiological evidence of pneumonia was seen in all studies, even in the presence of mild symptoms as reported by most [11,23-31]. Consolidation and ground-glass opacities are the most common imaging findings. Korea Centers for Disease Control and Prevention's (CDC&P) study reported only 32% of patients having fever but confirmed pneumonia on imaging once hospitalized in 68% of their cohort [31]. Most studies reported bilateral involvement, with Wang et al. reporting 100% of their cases with bilateral disease [25]. Table 2 summarizes patient radiological findings as reported in previous studies.

Laboratory findings include lymphopenia and raised C-reactive protein, Prothrombin time, D-dimer level and Procalcitonin [22,28].

6. RESOURCE LIMITATIONS MAY REQUIRE PRIORITIZATION OF LABORATORY TESTING

The suspicion of COVID-19 should be raised in patients with new-onset fever, respiratory tract symptoms, severe lower respiratory tract illness without an identifiable cause, residence in or travel to a high distribution area of COVID-19 and history of close contact with a suspected or confirmed case of COVID-19 [32]. Consultation over the phone regarding the need for diagnostic testing is encouraged [32].

Definitive diagnosis can only be made after molecular testing and this may not be possible for all cases due to limited capacity [32]. In this regard, the Infectious Diseases Society of America suggests a hierarchical approach demonstrated in Table 3 [33].

Patients who satisfy the above criteria should undergo testing for both COVID-19 as well as other respiratory pathogens (eg, influenza, respiratory syncytial virus) [32].

Laboratory diagnosis for COVID-19 requires SARS-CoV-2 RNA to be detected by reverse-transcription polymerase chain reaction (RT-PCR) from nasopharyngeal/ oropharyngeal swabs or bronchoalveolar lavage [1]. In the case of a negative test but persistent clinical suspicion resampling and testing from multiple respiratory sites is recommended [34].
Table 1. Summary of demographic findings of eleven early COVID-19 studies from China and South Korea

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Table 2. Summary of patient radiological findings as reported in previous COVID-19 studies

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<td>Radiographic evidence of pneumonia</td>
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<td>Yes</td>
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<td>Yes</td>
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| High Priority patients | Critically ill patients with viral pneumonia of unidentified causes or respiratory failure  
Symptomatic individuals with close contact with laboratory confirmed cases of COVID-19 within the last 14 days (Includes health care workers and residents of long-term care facilities with confirmed cases)  
Symptomatic individuals who are immunocompromised, elderly or have underlying health conditions  
Symptomatic individuals who are critical to the pandemic response, including health care workers, public health officials, and other essential leaders |
| Second-Priority     | Symptomatic patients with unexplained underlying cause who are hospitalized in a non-ICU setting or are residents of long-term care facility.                                                                                           |
| Third-Priority      | Outpatients who meet criteria for influenza testing (Flu-like symptoms plus comorbid conditions, such as diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, age >50 years, immunocompromising conditions).  
Outpatient pregnant women and symptomatic children with similar risk factors.                                                                                                                                 |
| Fourth Priority     | Community surveillance                                                                                                                                                                                                 |
7. CLINICAL TRIALS ARE UNDERWAY TO RECOGNIZE POTENTIAL THERAPEUTIC AGENTS AND DEVELOP A VACCINE

Currently, the main treatment strategies are symptomatic management and supportive care. This includes maintaining vital signs and oxygen saturation and treating complications such as secondary infections and organ failure [1,4]. Supportive measures for complicated patients include mechanical ventilation, continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) [4].

Efforts to develop a vaccine are currently in progress but it is expected to take 18 months for a vaccine to become available [4]. Numerous agents with possible therapeutic roles have been suggested and clinical trials are currently underway. Remdesivir is one of such agents recognized [35]; It is an experimental nucleotide analog being developed to treat Ebola. It has been shown to be efficacious against SARS-CoV and MERS-CoV in tissue cultures and non-human animal models [35]. Antivirals such as lopinavir/ ritonavir and interferon beta have been shown to have therapeutic value against SARS-CoV and thus may have a role in SARS-CoV-2 as well [35]. Other drugs being explored include chloroquine, arbidol and favipiravir [36]. Passive immunization with plasma from recovered COVID-19 patients has also been suggested as well [1]. Given the lack of proven therapeutic agents, uncertainty regarding the availability of a vaccine and the massive morbidity and mortality that has so far occurred it is imperative for the general population to practice social distancing, self-isolation, and quarantine as well as regular hand washing to prevent further spread of disease.

8. CONCLUSION

COVID-19 presents itself as an existential threat and challenges the global community economically, medically, and socially. Its containment demands our immediate attention. While we continue to see acts of valor by medical professionals, law enforcement and day to day essential workers, it is imperative that every individual takes up responsibility by engaging in hygienic practices, stopping social stigma and curbing the spread of misinformation.

As countries individually ramp up measures to contain the virus, the world needs to come together to assist each other, protect those most vulnerable and establish procedures and policies to stop the further spread of disease and ensure the prevention of future pandemics.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

 Authors have declared that no competing interests exist.

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